PATENT SPECIFICATION

NO DRAWINGS

872,352

Date of Application and filing Complete Specification: March 10, 1960
No. 8561/60.
Two Applications made in United States of America on March 26, 1959.
Application made in United States of America on June 22, 1959.
Five Applications made in United States of America on Oct. 12, 1959.
Three Applications made in United States of America on Nov. 16, 1959.
Complete Specification Published: July 5, 1961.

Index at acceptance:—Class 2(3), B4(A1: L), C1C(2: 3: 4: 9: 10: 11F: 11G), C1D, C1E(5K4: 6K4: 7K4), C1J1(C2: E), C2B(20: 50A4), C2D43(F: S2), C3A12(A4A: A4C: B3: B4: B6: C1: C6), C3A13A3(A4: B2: C: F3: L), C3A13C(1C: 2C: 3C: 9: 10F: 10H), C3A14A(3D: 5: 8A: 8D), C3A14B(3D: 5: 8A: 8D), C3C5(A4: C5: C7: E2), C3C6.

International Classification:—C07d.

COMPLETE SPECIFICATION

1-Arylalkyl-4-Arylpiperazines

SPECIFICATION NO. 872,352

By a direction given under Section 17(1) of the Patents Act 1949 this application ...ceeded in the name of N.V. Research Laboratorium Dr. C. Janssen, a Belgium Limited ...ability Company, of Turnhoutse Baan 30, Beerse, Turnhout, Belgium.

... PATENT OFFICE

DS 61433/1(2)/R.153 200 2/62 PL

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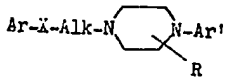
formula:



and the pharmaceutically acceptable non-toxic salts thereof. In this formula Ar is a halophenyl radical (such as fluorophenyl, chlorophenyl, bromophenyl and iodophenyl), an alkoxyphenyl radical (such as methoxyphenyl, ethoxyphenyl, dimethoxyphenyl and trimethoxyphenyl), a phenyl, tolyl or xylyl radical, or a thienyl radical. Ar^1 is a halophenyl radical (such as fluorophenyl, chlorophenyl, bromophenyl and iodophenyl), an alkoxyphenyl radical (such as methoxyphenyl, ethoxyphenyl, dimethoxyphenyl and trimethoxyphenyl), a phenyl, tolyl or xylyl radical, a benzoyl, a halobenzoyl (such as fluorobenzoyl, chlorobenzoyl, bromobenzoyl, iodobenzoyl), an alkoxybenzoyl (such as dimethoxybenzoyl, methoxybenzoyl and trimethoxybenzoyl), a trifluoromethylbenzoyl, a thenoyl, a pyridyl, a methylpyridyl, a pyrimidyl, a methylpyrimidyl, a nicotinyl, a 2-thiazolyl, a 2-methylthiazolyl, a 2 - (1,3,4-thiadiazolyl), a 5 - (1,2,4 - thiadiazolyl), a methylthiadiazolyl, a cyanopyridyl, a carboxamidopyridyl, a dimethylpyrimidyl, a methylthiopyridazino, a chloropyridazino, or a

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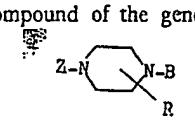
... and related acids. They also form quaternary ammonium salts with a variety of organic esters of sulphuric, hydrohalic and aromatic sulphonic acids. Among such esters are methyl chloride and bromide, ethyl chloride, propyl chloride, butyl chloride, isobutyl chloride, benzyl chloride and bromide, phenethyl bromide, naphthylmethyl chloride, dimethyl sulphate, diethyl sulphate, methyl benzenesulphonate, ethyl toluenesulphonate, ethylene chlorohydrin, propylene chlorohydrin, allyl bromide, methallyl bromide and crotyl bromide.

The compounds of this invention are useful because they are potent depressors of the central nervous system. Specifically, they are useful as barbiturate potentiators.

The process for the preparation of these compounds is accomplished by heating a compound of the general formula:

Ar—Y

with a compound of the general formula:



In these formulae, Ar and R are defined as above; B is hydrogen or Ar^1 (as defined as

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International Classification:—C07d.

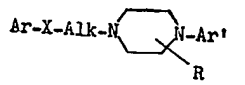
COMPLETE SPECIFICATION

1-Arylalkyl-4-Arylpiperazines

I, PAUL ADRIAAN JAN JANSSEN, a Citizen of Belgium, of Antwerpse Steenweg 16¹, Vosselaar near Turnhout, Belgium, do hereby declare the invention, for which I pray that a patent may be granted to me and the method by which it is to be performed, to be particularly described in and by the following statement:—

This invention relates to a new group of piperazine derivatives.

The present invention provides new 1-arylalkyl - 4 - arylpiperazines of the general formula:



and the pharmaceutically acceptable non-toxic salts thereof. In this formula Ar is a halophenyl radical (such as fluorophenyl, chlorophenyl, bromophenyl and iodophenyl), an alkoxyphenyl radical (such as methoxyphenyl, ethoxyphenyl, dimethoxyphenyl and trimethoxyphenyl), a phenyl, tolyl or xylyl radical, or a thienyl radical. Ar^1 is a halophenyl radical (such as fluorophenyl, chlorophenyl, bromophenyl and iodophenyl), an alkoxyphenyl radical (such as methoxyphenyl, ethoxyphenyl, dimethoxyphenyl and trimethoxyphenyl), a phenyl, tolyl or xylyl radical, a benzoyl, a halobenzoyl (such as fluorobenzoyl, chlorobenzoyl, bromobenzoyl, iodobenzoyl), an alkoxybenzoyl (such as dimethoxybenzoyl, methoxybenzoyl and trimethoxybenzoyl), a trifluoromethylbenzoyl, a thenoyl, a pyridyl, a methylpyridyl, a pyrimidyl, a methylpyrimidyl, a nicotinyl, a 2-thiazolyl, a 2-methylthiazolyl, a 2 - (1,3,4-thiadiazolyl), a 5 - (1,2,4 - thiadiazolyl), a methylthiadiazolyl, a cyanopyridyl, a carboxamidopyridyl, a dimethylpyrimidyl, a methylthiopyridazino, a chloropyridazino, or a methoxypyridazino radical. Alk is an alkylene radical of 3 or 4 atoms (such as propylene, trimethylene, methylpropylene and tetramethylene). R is hydrogen or a methyl radical and X is a carbonyl or a hydroxymethylene radical.

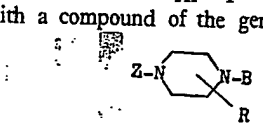
The organic bases of this invention form pharmaceutically acceptable non-toxic salts with a variety of inorganic and strong organic acids including sulphuric, phosphoric, hydrochloric, hydrobromic, hydriodic, sulphamic, citric, lactic, maleic, malic, succinic, tartaric, cinnamic, acetic, benzoic, gluconic, ascorbic and related acids. They also form quaternary ammonium salts with a variety of organic esters of sulphuric, hydrohalic and aromatic sulphonic acids. Among such esters are methyl chloride and bromide, ethyl chloride, propyl chloride, butyl chloride, isobutyl chloride, benzyl chloride and bromide, phenethyl bromide, naphthylmethyl chloride, dimethyl sulphate, diethyl sulphate, methyl benzenesulphonate, ethyl toluenesulphonate, ethylene chlorohydrin, propylene chlorohydrin, allyl bromide, methallyl bromide and crotyl bromide.

The compounds of this invention are useful because they are potent depressors of the central nervous system. Specifically, they are useful as barbiturate potentiators.

The process for the preparation of these compounds is accomplished by heating a compound of the general formula:

Ar—Y

with a compound of the general formula:



In these formulae, Ar and R are defined as above; B is hydrogen or Ar^1 (as defined as

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above); Y is —X—Alk—Halogen or Mg—Halogen; and Z is hydrogen or, in the case where Y is Mg—Halogen, it is NC—Alk—. In the case wherein B is hydrogen, B can be replaced by Ar^1 by reacting the product with a compound of the structural formula:

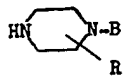
Halogen—Ar^1

wherein Ar^1 is defined as above.

Specifically, when the compounds of this invention are prepared by the condensation of a compound of the general formula:

Ar—X—Alk—Halogen

with a compound of the general formula:

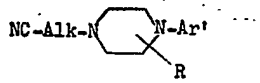


wherein Alk, Ar, B, R, and X are defined as above, the reaction is conveniently carried out in an inert solvent such as an aromatic hydrocarbon (e.g. benzene, toluene, xylene), an alkenol (e.g. ethanol, propanol, butanol), or an alkanone (e.g. butanone, pentanone). The reaction can be accelerated by using elevated temperature and elevated pressures.

It is an obvious equivalent to those skilled in the art to form a compound wherein B is hydrogen and then to react the product with an appropriately selected compound of the general formula:

Halogen—Ar^1

The modification of the process in which Y is defined as Mg—Halogen and Z is defined as NC—Alk is carried out by heating a 4-aryl - 1 - piperazinealkanonitrile of the general formula:

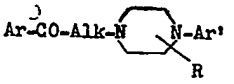


with an arylmagnesium halide of the general formula:

Ar—Mg—Halogen

under typical Grignard conditions, followed by an acid hydrolysis of the adduct.

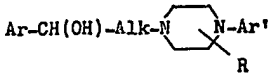
The compounds of the general formula:



can be reduced by using a metal hydride of the general formula:

(alkali metal)MH_4

where M is an element of Periodic Group III of atomic number less than 14 (i.e. boron or aluminium) to form compounds of the general formula:

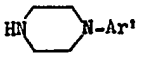


The intermediates of the general formula:

Ar—X—Alk—Halogen

are prepared conveniently by conventional methods, such as a mild variation of the Friedel-Craft reaction; for example, where X is carbonyl, using γ-chlorobutyryl chloride in benzene or an appropriately substituted benzene such as toluene, xylen, halogenated benzene or an alkoxy benzene.

The compounds of the general formula:



used as intermediates in this process are prepared by the condensation of piperazine and an appropriate compound of the general formula:

Ar^1—Halogen

The following Examples illustrate some of the compounds which comprise this invention and the processes for their production. In these Examples quantities of materials are given in parts by weight, pressures in millimetres (mm.) of mercury, and temperature in degrees Centigrade (°C.).

EXAMPLE 1.

A mixture of 7.5 parts of γ-chlorobutyrophenone and 13.4 parts of 1-phenylpiperazine was allowed to remain at room temperature for 6 hours. The reaction was then continued by heating the mixture for 4 hours at a temperature of 105—110° C. After cooling to room temperature, 200 parts of ether were added, and the mixture was washed with water. The ethereal solution was dried over anhydrous potassium carbonate, filtered, and evaporated. The residue was taken up in a 4:1 mixture of 70% ethanol and ether. The solution was cooled and the precipitate thus obtained was recovered by filtration and recrystallised first from a 6:5 mixture of 2-propanol and water. The 1 - (γ - benzoylpropyl) - 4 - phenylpiperazine thus obtained melted at about 89—90° C. The hydrochloride of this compound was obtained by saturating an ethereal solution of the base with hydrogen chloride gas and collecting the precipitate.

EXAMPLE 2.

By substituting the appropriate starting materials in the procedure of Example 1, the following compounds were obtained.

1 - (δ - Benzoylbutyl) - 4 - phenylpiperazine dihydrochloride melting at about 209—212° C. after recrystallisation from an 8:8:1 mixture of acetone, 2-propanol, and methanol.

1 - (γ - Benzoylpropyl) - 4 - (3 - fluorophenyl)piperazine melting at about 80.2—81.6° C. after recrystallisation from diisopropyl ether.

1 - (γ - Benzoylpropyl) - 4 - (3 - chlorophenyl)piperazine melting at about 88—90° C.

1 - (γ - Benzoylpropyl) - 4 - (4 - chlorophenyl)piperazine melting at about 127—128.4° C. after recrystallisation from a 10:1 mixture of petroleum ether and ethanol.

1 - (γ - Benzoylpropyl) - 4 - (2 - tolyl)-piperazine hydrochloride melting at about 205—207° C. after recrystallisation from a 5:4:3 mixture of 2-propanol, methanol and

acetone.

1 - (γ - Benzoylpropyl) - 4 - (3 - tolyl)-piperazine melting at about 78—79° C. after recrystallisation from a 13:1 mixture of petroleum ether and ethanol.

1 - (γ - Benzoylpropyl) - 4 - (4 - tolyl)-piperazine melting at about 87.5—88.3° C. after recrystallisation from 2-propanol and water.

1 - (γ - Benzoylpropyl) - 4 - (2,5 - xylyl)-piperazine hydrochloride melting at about 229—230° C.

1 - (γ - Benzoylpropyl) - 4 - (2 - anisyl)-piperazine dihydrochloride melting at about 207.5—209.5° C. after recrystallisation from 2-propanol.

1 - (γ - Benzoylpropyl) - 4 - (4 - anisyl)-piperazine melting at about 85—86.2° C. after recrystallisation from diisopropyl ether.

1 - [γ - (4 - Fluorobenzoyl)propyl] - 4-phenylpiperazine melting at about 104—106° after recrystallisation from 2-propanol.

1 - [γ - (4 - Fluorobenzoyl)propyl] - 4-(3 - fluorophenyl) piperazine dihydrochloride melting at about 198—200° C.

1 - [γ - (4 - Fluorobenzoyl)propyl] - 4-(4 - fluorophenyl) - piperazine dihydrochloride melting at about 199.5—202.1° C.

1 - [γ - (4 - Fluorobenzoyl)propyl] - 4-(4 - fluorophenyl) - piperazine hydrochloride melting at about 180.2—181.6° C. after recrystallisation from a 1:3 mixture of acetone and 2-propanol.

1 - [γ - (4 - Fluorobenzoyl)propyl] - 4-(2 - chlorophenyl) - piperazine hydrochloride melting at about 211—214° C. after recrystallisation from 2-propanol.

1 - [γ - (4 - Fluorobenzoyl)propyl] - 4-(3 - chlorophenyl) - piperazine hydrochloride melting at about 197.8—199.5° C. after recrystallisation from a mixture of acetone and methanol.

1 - [γ - (4 - Fluorobenzoyl)propyl] - 4-(4 - chlorophenyl) - piperazine melting at about 96—98° C. after recrystallisation from a 40:3 mixture of petroleum ether and ethanol.

1 - [γ - (4 - Fluorobenzoyl)propyl] - 4-(2 - tolyl)piperazine hydrochloride melting at about 238—241° C. with decomposition after recrystallisation from a 1:2 mixture of acetone and methanol.

1 - [γ - (4 - Fluorobenzoyl)propyl] - 4-(3 - tolyl)piperazine dihydrochloride melting at about 210—213° C. with decomposition after recrystallisation from a mixture of acetone and methanol.

1 - [γ - (4 - Fluorobenzoyl)propyl] - 4-(4 - tolyl)piperazine melting at about 99—101° C. after recrystallisation from 2-propanol and water.

1 - [γ - (4 - Fluorobenzoyl)propyl] - 4-(2,5 - xylyl)piperazine dihydrochloride melting at about 237.5—239.5° C. after recrystallisation from 2-propanol and methanol.

1 - [γ - (4 - Fluorobenzoyl)propyl] - 4-(2 - anisyl)piperazine dihydrochloride melting at about 205—205.5° C.

1 - [γ - (4 - Fluorobenzoyl)propyl] - 4-(2 - anisyl)piperazine melting at about 67.5—68.5° C. after recrystallisation with diisopropyl ether.

1 - [γ - (4 - Fluorobenzoyl)propyl] - 4-(4 - anisyl)piperazine melting at about 104.6—105.6° C. after recrystallisation from 2-propanol.

1 - [γ - (4 - Fluorobenzoyl)propyl] - 4-phenylpiperazine melting at about 113.5—114.4° C. after recrystallisation from a mixture of acetone and methanol.

1 - [γ - (4 - Fluorobenzoyl)propyl] - 4-(3 - chlorophenyl)piperazine melting at about 86—88° C. after recrystallisation from diisopropyl ether.

1 - [γ - (4 - Fluorobenzoyl)propyl] - 4-(3 - tolyl)piperazine melting at about 99.6—110.4° C. after recrystallisation from diisopropyl ether.

1 - [γ - (4 - Fluorobenzoyl)propyl] - 4-(4 - tolyl)piperazine melting at about 129.5—130.5° C. after recrystallisation from diisopropyl ether.

1 - [γ - (4 - Fluorobenzoyl)propyl] - 4-(4 - anisyl)piperazine melting at about 126.6—127.8° C. after recrystallisation from diisopropyl ether.

1 - [γ - (4 - Methylbenzoyl)propyl] - 4-phenylpiperazine melting at about 103—104.8° C. after recrystallisation from a 10:7 mixture of petroleum ether and ethanol.

1 - [γ - (4 - Methylbenzoyl)propyl] - 4-(2 - chlorophenyl)piperazine melting at about 106—107° C. after recrystallisation from water and 2-propanol.

1 - [γ - (4 - Methylbenzoyl)propyl] - 4-(3 - chlorophenyl)piperazine melting at about 124.5—125.5° C. after recrystallisation from a mixture of acetone and methanol.

1 - [γ - (4 - Methylbenzoyl)propyl] - 4-(4 - chlorophenyl)piperazine melting at about 134.5—136° C. after recrystallisation from a 3:2 mixture of 2-propanol and water.

1 - [γ - (4 - Methylbenzoyl)propyl] - 4-(3 - tolyl)piperazine melting at about 87—88.5° C. after recrystallisation from a 2:1 mixture of 2-propanol and water.

1 - [γ - (4 - Methylbenzoyl)propyl] - 4-(4 - tolyl)piperazine melting at about 117.2—119.2° C. after recrystallisation from a 7:5 mixture of methanol and acetone.

1 - [γ - (4 - Methylbenzoyl)propyl] - 4-(4 - anisyl)piperazine melting at about 123.2—124° C. after recrystallisation from diisopropyl ether.

1 - [γ - (2,5 - Dimethylbenzoyl)propyl] - 4-phenylpiperazine hydrochloride melting at about 179.5—180.5° C.

1 - [γ - (4 - Anisoyl)propyl] - 4 - (3-fluorophenyl)piperazine melting at about 111—113°C. after recrystallisation from diisopropyl ether.

1 - [γ - (4 - Anisoyl)propyl] - 4 - (2-chlorophenyl)piperazine melting at about 73.5—73.8° C. after recrystallisation from diisopropyl ether.

1 - [γ - (4 - Anisoyl)propyl] - 4 - (3-iodophenyl)piperazine after recrystallisation from diisopropyl ether.

1 - [γ - (4 - Anisoyl)propyl] - 4 - (3-chlorophenyl)piperazine melting at about 101.6—102.4° C. after recrystallisation from a mixture of 2-propanol and water.

1 - [γ - (4 - Anisoyl)propyl] - 4 - (4-chlorophenyl)piperazine melting at about 128.6—130° C. after recrystallisation from 2-propanol.

1 - [γ - (4 - Anisoyl)propyl] - 4 - (2-tolyl)piperazine hydrochloride melting at about 239.5—240.5° C. after recrystallisation from a mixture of acetone and methanol.

1 - [γ - (4 - Anisoyl)propyl] - 4 - (3-tolyl)piperazine melting at about 105—106° C. after recrystallisation from a mixture of 2-propanol and water.

1 - [γ - (4 - Anisoyl)propyl] - 4 - (4-tolyl)piperazine melting at about 126.6—127.6° C. after recrystallisation from a 2:1 mixture of 2-propanol and water.

1 - [γ - (4 - Anisoyl)propyl] - 4 - (2,5-xylyl)piperazine hydrochloride melting at about 225—226° C. after recrystallisation from 2-propanol.

1 - [γ - (4 - Anisoyl)propyl] - 4 - (2-anisyl)piperazine dihydrochloride melting at about 197—198.2° C. after recrystallisation from 2-propanol.

1 - [γ - (4 - Anisoyl)propyl] - 4 - (4-anisyl)piperazine melting at about 125.6—127.4° C. after recrystallisation from 2-propanol.

1 - [γ - (2,4 - Dimethoxybenzoyl)propyl]-4 - phenylpiperazine dihydrochloride melting at about 195—196° C. after recrystallisation from a mixture of acetone and 2-propanol.

1 - [γ - (3,4 - Dimethoxybenzoyl)propyl]-4 - phenylpiperazine melting at about 101—103.5° C. after recrystallisation from diisopropyl ether.

1 - [γ - (2,4 - Dimethoxybenzoyl)propyl]-4 - (2 - tolyl)piperazine hydrochloride melting at about 177—179.2° C. after recrystallisation from 2-propanol.

1 - [γ - (2,4 - Dimethoxybenzoyl)propyl]-4 - (2 - anisyl)piperazine hydrochloride melting at about 214—215° C. after recrystallisation from a mixture of 2-propanol and acetone.

1 - [γ - (2,5 - Dimethoxybenzoyl)propyl]-4 - phenylpiperazine dihydrochloride decomposing at about 179—180° C.

1 - [γ - (2,3,4 - Trimethoxybenzoyl)propyl]-4 - phenylpiperazine melting at about 113—116.2° C. after recrystallisation from acetone.

1 - [γ - (4 - Ethoxybenzoyl)propyl] - 4-phenylpiperazine melting at about 125.2—126.8° C. after recrystallisation from diisopropyl ether.

1 - [γ - (4 - Ethoxybenzoyl)propyl] - 4-(3 - tolyl)piperazine melting at about 113.4—113.8° C. after recrystallisation from 2-propanol.

1 - (β - Methyl - γ - benzoylpropyl) - 4-phenylpiperazine dihydrochloride melting at about 219.5—221.5° C. after recrystallisation from 2-propanol.

1 - (β - Methyl - γ - benzoylpropyl) - 4-(3 - tolyl)piperazine melting at about 32.8—33.8° C. after recrystallisation from petroleum ether.

1 - (β - Methyl - γ - benzoylpropyl) - 4-(2 - anisyl)piperazine dihydrochloride melting at about 193—197° C. after recrystallisation from a mixture of acetone and 2-propanol.

1 - (δ - Benzoylbutyl) - 4 - (3 - tolyl)-piperazine dihydrochloride melting at about 191.5—192.5° C. after recrystallisation from a mixture of 2-propanol and methanol.

1 - [γ - (4 - Chlorobenzoyl)propyl] - 4-(4 - fluorophenyl)piperazine hydrochloride melting at about 207—209° C. after recrystallisation from a mixture of acetone and 2-propanol.

1 - [γ - (4 - Chlorobenzoyl)propyl] - 4-(4 - chlorophenyl)piperazine melting at about 127—128.5° C. after recrystallisation from a mixture of diisopropyl ether and acetone.

1 - (δ - Benzoylbutyl) - 4 - (2 - pyridyl)-piperazine dihydrochloride melting at about 206.5—207.5° C. after recrystallisation from a 4:2:1 mixture of 2-propanol, acetone, and methonol.

1 - (γ - Benzoylpropyl) - 4 - (2 - pyridyl)-piperazine melting at about 63—64.8° C.

1 - [γ - (4 - Methylbenzoyl)propyl] - 4-(2-pyridyl)piperazine melting at about 92—93° C.

1 - [γ - (3,4 - Dimethoxybenzoyl)propyl]-4 - (2 - pyridyl)piperazine melting at about 104.5—106.9° C. after recrystallisation from acetone.

1 - (γ - Benzoylpropyl) - 4 - (6 - methyl-2 - pyridyl)piperazine melting at about 72—75.8° C. after recrystallisation from petroleum ether.

1 - (γ - Benzoylpropyl) - 4 - (4 - methyl-2 - pyridyl)piperazine melting at about 65.5—66.5° C. after recrystallisation from diisopropyl ether.

1 - (γ - Benzoylpropyl) - 4 - (3 - cyano - 2-pyridyl)piperazine melting at about 45.5—47° C. after recrystallisation from diisopropyl ether.

1 - (γ - Benzoylpropyl) - 4 - (5 - methyl-2 - pyridyl)piperazine melting at about 71.5—73° C. after recrystallisation from diisopropyl ether.

1 - [γ - (4 - Fluorobenzoyl)propyl] - 4-(5 - methyl - 2 - pyridyl)piperazine melting at about 92—93° C. after recrystallisation from diisopropyl ether.

1 - [γ - (4 - Iodobenzoyl)propyl] - 4 - (5-

methyl - 2 - pyridyl)piperazine after recrystallisation from diisopropyl ether.

1 - [γ - (4 - Chlorobenzoyl)propyl] - 4 - (2 - pyridyl)piperazine melting at about 82.5—84.4° C.

1 - [γ - (4 - Iodobenzoyl)propyl] - 4 - (2-pyridyl)piperazine.

1 - [γ - (4 - Methoxybenzoyl)propyl] - 4-(6 - methyl - 2 - pyridyl)piperazine melting at about 74—76° C. after recrystallisation from diisopropyl ether and petroleum ether.

1 - [γ - (4 - Methoxybenzoyl)propyl] - 4-(4 - methyl - 2 - pyridyl)piperazine melting at about 69.5—70.5° C. after recrystallisation from diisopropyl ether.

1 - [γ - (4 - Methoxybenzoyl)propyl] - 4-(5 - methyl - 2 - pyridyl)piperazine melting at about 84.6—86° C.

1 - [γ - (2,4 - Dimethoxybenzoyl)propyl]-4 - (2 - pyridyl)piperazine melting at about 84.5—85.5° C. after recrystallisation from diisopropyl ether.

1 - [γ - (3,4 - Dimethoxybenzoyl)propyl]-4 - (4 - methyl - 2 - pyridyl)piperazine melting at about 85.4—86.5° C. after recrystallisation from diisopropyl ether.

1 - [γ - (2,4 - Dimethoxybenzoyl)propyl]-4 - (4 - methyl - 2 - pyridyl)piperazine melting at about 79—80.8° C. after recrystallisation from diisopropyl ether.

1 - [γ - (4 - Methoxybenzoyl)propyl] - 4-(3 - cyano - 2 - pyridyl)piperazine melting at about 73.5—75.5° C. after recrystallisation from diisopropyl ether.

1 - [γ - (2 - Thenoyl)propyl] - 4 - (2-pyridyl)piperazine melting at about 70—71° C.

1 - [γ - (2 - Thenoyl)propyl] - 4 - (5-methyl - 2 - pyridyl)piperazine melting at about 89.5—90.5° C. after recrystallisation from diisopropyl ether.

1 - [γ - (2 - Thenoyl)propyl] - 4 - (4-methyl - 2 - pyridyl)piperazine melting at about 65—66° C. after recrystallisation from diisopropyl ether.

1 - [γ - (2 - Thenoyl)propyl] - 4 - (6-methyl - 2 - pyridyl)piperazine melting at about 107.5—108.5° C.

1 - [γ - (2 - Thenoyl)propyl] - 4 - (3-cyano - 2 - pyridyl)piperazine melting at about 71.5—72.5° C. after recrystallisation from diisopropyl ether.

1 - (γ - Benzoylpropyl) - 4 - (2 - pyrimidyl)-piperazine melting at about 78—79° C.

1 - [γ - (4 - Methylbenzoyl)propyl] - 4 - (2-pyrimidyl)piperazine.

1 - (δ - Benzoylbutyl) - 4 - (2 - pyrimidyl)-piperazine.

1 - (γ - Benzoylpropyl) - 4 - (4 - methyl-2 - pyrimidyl)piperazine melting at about 62.4—63.2° C.

1 - (γ - Benzoylpropyl) - 4 - (4,6 - dimethyl-2 - pyrimidyl)piperazine melting at about 97.4—98° C. after recrystallisation from diisopropyl ether.

1 - [γ - (4 - Fluorobenzoyl)propyl] - 4-(4 - methyl - 2 - pyrimidyl)piperazine dihydrochloride melting at about 215—220° C. after recrystallisation from 2-propanol and ethanol.

1 - [γ - (4 - Iodobenzoyl)propyl] - 4 - (4-methyl - 2 - pyrimidyl)piperazine dihydrochloride after recrystallisation from 2-propanol and ethanol.

1 - [γ - (4 - Fluorobenzoyl)propyl] - 4-(4,6 - dimethyl - 2 - pyrimidyl)piperazine melting at about 85.5—87.5° C. after recrystallisation from diisopropyl ether.

1 - [γ - (4 - Methoxybenzoyl)propyl] - 4-(2 - pyrimidyl)piperazine melting at about 83—83.5° C. after recrystallisation from diisopropyl ether.

1 - [γ - (4 - Methoxybenzoyl)propyl] - 4-(4 - methyl - 2 - pyrimidyl)piperazine dihydrochloride melting at about 90° C.

1 - [γ - (4 - Methoxybenzoyl)propyl] - 4-(4,6 - dimethyl) - 2 - pyrimidyl)piperazine melting at about 71.8—74.2° C.

1 - [γ - (2 - Thenoyl)propyl] - 4 - (2-pyrimidyl)piperazine melting at about 57.5—58.6° C.

1 - [γ - (2 - Thenoyl)propyl] - 4 - (4-methyl - 2 - pyrimidyl)piperazine melting at about 52—53° C. after recrystallisation from diisopropyl ether.

1 - [γ - (2 - Thenoyl)propyl] - 4 - (4-methyl - 2 - pyrimidyl)piperazine dihydrochloride melting at about 214.8—217° C. after recrystallisation from 2-propanol.

1 - [γ - (2 - Thenoyl)propyl] - 4 - (4,6-dimethyl - 2 - pyrimidyl)piperazine melting at about 64.5—65.6° C. after recrystallisation from a mixture of diisopropyl ether and petroleum ether.

1 - [γ - (4 - Fluorobenzoyl)propyl] - 4 - (2-pyrimidyl)piperazine melting at about 111.6—112.8° C. after recrystallisation from diisopropyl ether.

1 - (γ - Benzoylpropyl) - 4 - (2 - thiazolyl)-piperazine melting at about 61.5—64° C. after recrystallisation from diisopropyl ether.

1 - (δ - Benzoylbutyl) - 4 - (2 - thiazolyl)-piperazine recrystallised from diisopropyl ether.

1 - (γ - Benzoylpropyl) - 4 - [2 - (4-methyl)thiazolyl]piperazine dihydrochloride melting at about 186—188.6° C. after recrystallisation from a 10:3 mixture of ethanol and methanol.

1 - [γ - (4 - Fluorobenzoyl)propyl] - 4-(2 - thiazolyl)piperazine melting at about 74.5—76.5° C. after recrystallisation from diisopropyl ether.

1 - [γ - (4 - Iodobenzoyl)propyl] - 4-(2 - thiazoyl)piperazine recrystallised from diisopropyl ether.

1 - [γ - (4 - Fluorobenzoyl)propyl] - 4-[2 - (5 - methyl) - thiazolyl]piperazine melting at about 73—75.2° C. after recrystallisation from diisopropyl ether.

1 - [γ - (4 - Methoxybenzoyl)propyl] - 4-

(2 - thiazolyl)piperazine dihydrochloride melting at about 122.4° C. after recrystallisation from a 7:3 mixture of 2-propanol and ethanol.

1 - [γ - (4 - Methoxybenzoyl)propyl] - 4-[2 - (4 - methyl) - thiazolyl]piperazine melting at about 62.5—72° C.

1 - [γ - (4 - Methoxybenzoyl)propyl] - 4-[2 - (4 - methyl) - thiazolyl]piperazine dihydrochloride melting at about 187—201° C. after recrystallisation from a 2:5 mixture of ethanol and 2-propanol.

1 - [γ - (2 - Thenoyl)propyl] - 4 - (2-thiazolyl)piperazine melting at about 52.2—54.6° C. after recrystallisation from diisopropyl ether.

1 - [γ - (2 - Thenoyl)propyl] - 4 - [2-(4 - methyl)thiazolyl]piperazine dihydrochloride melting at about 163—176° C. after recrystallisation from ethanol.

1 - (γ - Benzoylpropyl) - 4 - [2 - (1,3,4-thiadiazolyl)]piperazine melting at about 59—64° C.

1 - (γ - Benzoylpropyl) - 4 - [2 - (5-methyl - 1,3,4 - thiadiazolyl)]piperazine melting at about 98—100.2° C. after recrystallisation from normal hexane.

1 - [γ - (4 - Fluorobenzoyl)propyl] - 4-[2 - (5 - methyl - 1,3,4 - thiadiazolyl)]piperazine melting at about 105—106° C. after recrystallisation from diisopropyl ether.

1 - [γ - (4 - Fluorobenzoyl)propyl] - 4-[2 - (1,3,4 - thiadiazolyl)]piperazine melting at about 94.6—95.8° C. after recrystallisation from diisopropyl ether.

1 - [γ - (4 - Methoxybenzoyl)propyl] - 4-[2 - (5 - methyl - 1,3,4 - thiadiazolyl)]piperazine melting at about 111.5—112.5° C. after recrystallisation from diisopropyl ether.

1 - [γ - (2 - Thenoyl)propyl] - 4 - [2-(5 - methyl - 1,3,4 - thiadiazolyl)]piperazine melting at about 83.6—85.6° C. after recrystallisation from *n*-heptane.

1 - [γ - (2 - Thenoyl)propyl] - 4 - phenylpiperazine hydrochloride melting at about 186—187° C. after recrystallisation from a mixture of acetone, 2-propanol, and methanol.

1 - [γ - (2 - Thenoyl)propyl] - 4 - (3-fluorophenyl)piperazine melting at about 68.2—70.2° C. after recrystallisation from diisopropyl ether.

1 - [γ - (2 - Thenoyl)propyl] - 4 - (2-chlorophenyl)piperazine hydrochloride melting at about 202.5—203° C. after recrystallisation from a mixture of acetone and 2-propanol.

1 - [γ - (2 - Thenoyl)propyl] - 4 - (3-chlorophenyl)piperazine melting at about 103.6—104.6° C. after recrystallisation from a mixture of 2-propanol and water.

1 - [γ - (2 - Thenoyl)propyl] - 4 - (4-chlorophenyl)piperazine melting at about 94.5—96.5° C. after recrystallisation from 2-propanol.

1 - [γ - (2 - Thenoyl)propyl] - 4 - (2-tolyl)piperazine hydrochloride melting at about 212—213° C. after recrystallisation from a mixture of acetone, 2-propanol, and methanol.

1 - [γ - (2 - Thenoyl)propyl] - 4 - (3-tolyl)piperazine melting at about 74—76° C. after recrystallisation from petroleum ether and ethanol.

1 - [γ - (2 - Thenoyl)propyl] - 4 - (4-tolyl)piperazine melting at about 77.5—78.5° C. after recrystallisation from a mixture of ethanol and water.

1 - [γ - (2 - Thenoyl)propyl] - 4 - (2,5-dimethylphenyl)piperazine dihydrochloride melting at about 214—215° C.

1 - [γ - (2 - Thenoyl)propyl] - 4 - (2-anisyl)piperazine dihydrochloride melting at about 197—201.8° C. after recrystallisation from a mixture of acetone and 2-propanol.

1 - [γ - (2 - Thenoyl)propyl] - 4 - (4-anisyl)piperazine melting at about 69—70° C. after recrystallisation from diisopropyl ether.

EXAMPLE 3.

A mixture of 9.1 parts of γ-chlorobutyrophenone, 23 parts of 1 - (4 - fluorophenyl)-piperazine, and 0.1 part of potassium iodide in 120 parts of toluene was heated in a sealed tube for 72 hours at a temperature of 145—150° C. cooled and partitioned between water and ether. The ether layer was separated, dried and filtered. Anhydrous hydrogen chloride gas was introduced into the filtrate and the resulting precipitate was collected on a filter and then recrystallised from a 1:2:2 mixture of acetone, 2-propanol and methanol to yield 1 - (γ - benzoylpropyl) - 4 - (4-fluorophenyl)piperazine dihydrochloride melting at about 214.5—217° C. The free base of this compound was obtained by dissolving the dihydrochloride in water and adding an excess of sodium hydroxide. The precipitate was collected on a filter and then recrystallised from ethanol to yield 1 - (γ - benzoylpropyl)-4 - (4 - fluorophenyl)piperazine melting at about 104—105.5° C.

EXAMPLE 4.

By substituting the appropriate starting materials in the procedure of Example 3, the following products were obtained:

1 - [γ - (4 - Anisoyl)propyl] - 4 - phenylpiperazine melting at about 126.6—127.5° C. after recrystallisation from diisopropyl ether.

1 - [γ - (4 - Anisoyl)propyl] - 4 - (4-fluorophenyl)piperazine melting at about 121.2—121.8° C. after recrystallisation from ethanol.

1 - [γ - (2 - Thenoyl)propyl] - 4 - phenylpiperazine dihydrochloride which, after recrystallisation from a mixture of acetone, 2-propanol and methanol, decomposes at 203—205° C.

1 - [γ - (2 - Thenoyl)propyl] - 4 - (4-fluorophenyl)piperazine melting at about 82.5—83° C. after recrystallisation from ethanol.

EXAMPLE 5.

A mixture of 4.4 parts of γ-chloro-4-fluoro-

butyro-phenone and 7.8 parts of 1-(3-methyl-2-pyridyl)piperazine in 120 parts of benzene was heated in a sealed tube for 24 hours at 125° C. After cooling the mixture was partitioned between water and benzene. The organic layer was separated, dried, filtered and evaporated. The residue was dissolved in diisopropyl ether. Hydrogen chloride gas was passed through the solution and the resulting precipitate was collected on a filter and then recrystallised from diisopropyl ether to yield 1 - [γ - (4 - fluorobenzoyl)propyl] - 4 -(3-methyl - 2 - pyridyl)piperazine hydrochloride, melting at about 212—220° C.

EXAMPLE 6.

By substituting the appropriate starting materials in the procedure of Example 5, the following products were obtained:

1 - [γ - (4 - Fluorobenzoyl)propyl] - 4-(4 - methyl - 2 - pyridyl)piperazine melting at about 79.5—81° C. after recrystallisation from diisopropyl ether.

1 - [γ - (4 - Fluorobenzoyl)propyl] - 4-(3 - cyano - 2 - pyridyl)piperazine melting at about 71.5—73.5° C. after recrystallisation from diisopropyl ether.

1 - [γ - (4 - Fluorobenzoyl)propyl] - 4-(6 - chloro - 3 - pyridazine)piperazine melting at about 152—153.9° C.

1 - [γ - (4 - Methoxybenzoyl)propyl] - 4-(6 - chloro - 3 - pyridazine)piperazine melting at about 176—176.8° C.

1 - [γ - (2 - Thenoyl)propyl] - 4 - (6-chloro - 3 - pyridazine)piperazine melting at about 138—138.8° C.

1 - [γ - (2 - Thenoyl)propyl] - 4 - (6-methoxy - 3 - pyridazine)piperazine melting at about 98.8—99.8° C.

EXAMPLE 7.

To a solution of 7 parts of 1 - (γ - benzoylpropyl)piperazine and 60 parts of benzene and 50 parts of a 10% aqueous sodium hydroxide solution were added 4.5 parts of benzoyl chloride with stirring. The mixture was heated slowly to about 70° C. for 45—60 minutes, cooled, and the layers separated. The water layer was extracted twice with benzene. The combined organic solutions were washed with water, dried, and evaporated. The residue was crystallised from diisopropyl ether by chilling to yield 1 - (γ - benzoylpropyl) - 4 - benzoylpiperazine melting at about 85—86° C.

EXAMPLE 8.

By substituting the appropriate starting materials in the procedure of Example 7, the following compounds were obtained:

1 - (γ - Benzoylpropyl) - 4 - (4 - fluorobenzoyl)piperazine hydrochloride melting at about 214.5—216.5° C.

1 - (γ - Benzoylpropyl) - 4 - (2 - chlorobenzoyl)piperazine hydrochloride melting at about 216—217.5° C.

1 - (γ - Benzoylpropyl) - 4 - (3 - chlorobenzoyl)piperazine hydrochloride melting at about 210.5—212.5° C.

1 - (γ - Benzoylpropyl) - 4 - (4 - chlorobenzoyl)piperazine melting at about 98—99° C.

1 - (γ - Benzoylpropyl) - 4 - (3 - trifluoromethylbenzoyl)piperazine melting at about 77.5—79° C.

1 - (γ - Benzoylpropyl) - 4 - (2 - anisoyl)-piperazine hydrochloride melting at about 140.8—143° C.

1 - (γ - Benzoylpropyl) - 4 - (2,6 - dimethoxybenzoyl)piperazine oxalate melting at about 193.1—194.8° C.

1 - (γ - Benzoylpropyl) - 4 - (3,4,5 - trimethoxybenzoyl)piperazine oxalate melting at about 187.4—188.2° C.

1 - [γ - (4 - Fluorobenzoyl)propyl] - 4-benzoylpiperazine hydrochloride melting at about 228—232.5° C.

1 - [γ - (4 - Anisoyl)propyl] - 4 - benzoylpiperazine hydrochloride melting at about 200.2—203.2° C.

1 - [γ - (4 - Anisoyl)propyl] - 4 - (4-fluorobenzoyl)piperazine melting at about 65.2—66.2° C.

1 - [γ - (4 - Anisoyl)propyl] - 4 - (2-anisoyl)piperazine melting at about 97—98.2° C.

1 - [γ - (4 - Anisoyl)propyl] - 4 - (2,6-dimethoxybenzoyl)piperazine oxalate melting at about 201.5—201.8° C.

1 - (γ - Benzoylpropyl) - 4 - [5 - (3-methyl - 1,2,4 - thiadiazolyl)]piperazine melting at about 78—79° C. after recrystallisation from diisopropyl ether.

1 - (γ - Benzoylpropyl) - 4 - (3 - carboxamido - 2 - pyridyl)piperazine melting at about 112.6—114.2° C. after recrystallisation from 2-propanol.

1 - [γ - (2 - Thenoyl)propyl] - 4 - (4-fluorobenzoyl)piperazine melting at about 82.5—83.5° C. after recrystallisation from ether.

1 - [γ - (2 - Thenoyl)propyl] - 4 - nicotinylpiperazine melting at about 64.6—65.8° C. after recrystallisation from ether.

1 - [γ - (2 - Thenoyl)propyl] - 4 - (2-thenoyl)piperazine melting at about 85.6—87.4° C. after recrystallisation from ether.

EXAMPLE 9.

To 8.5 parts of 1 - (γ - benzoylpropyl) - 4-phenyl - piperazine dissolved in 160 parts of absolute ethanol was added 0.25 part of sodium borohydride portionwise and with stirring. The stirring was continued for 2 hours at 45° C. The mixture was then decomposed with 2—N hydrochloric acid and the solvent was removed by distillation. After dissolving the residue in water, the solution was made alkaline with 5% sodium hydroxide and then extracted with ether. After drying, hydrogen chloride gas was passed through the ethereal solution. The dihydrochloride which precipitated was collected and recrystallised from a mixture of acetone, 2-propanol and methanol by chilling at −15° C. to yield 1 - phenyl - 4 - (4-

phenylpiperazine) - 1 - butanol dihydrochloride melting at about 198—200° C. The base of this compound was obtained by dissolving the salt in water, rendering the solution alkaline, extracting the solution with ether, and evaporating the ether extract.

EXAMPLE 10.

By substituting the appropriate starting materials in the procedure of Example 9, the following products were obtained:

1 - Phenyl - 5 - (4 - phenylpiperazine) - 1-pentanol melting at about 111—112° C. after recrystallisation from a mixture of acetone and water.

1 - Phenyl - 4 - [4 - (3 - tolyl)piperazine]-1 - butanol melting at about 83.5—84.5° C. after recrystallisation from diisopropyl ether.

1 - Phenyl - 4 - [4 - (4 - tolyl)piperazine]-1 - butanol melting at about 90.2—91.8° C. after recrystallisation from diisopropyl ether.

1 - Phenyl - 5 - [4 - (3 - tolyl)piperazine]-1-pentanol melting at about 107.4—109.2° C.

1 - Phenyl - 4 - [4 - (3 - fluorophenyl)-piperazine] - 1 - butanol melting at about 70—71.5° C. after recrystallisation from diisopropyl ether.

1 - Phenyl - 4 - [4 - (3 - chlorophenyl)-piperazine] - 1 - butanol melting at about 99—99.9° C. after purifying with diisopropyl ether.

1 - Phenyl - 4 - [4 - (4 - chlorophenyl) piperazine] - 1 - butanol melting at about 105—106° C. after recrystallisation from a mixture of diisopropyl ether and acetone.

1 - Phenyl - 4 - [4 - (4 - Anisyl)piperazine]-1 - butanol melting at about 91.5—92.6° C. after recrystallisation from diisopropyl ether.

1 - (4 - Tolyl) - 4 - (4 - phenylpiperazine)-1 - butanol melting at about 104.8—105.6° C. after purifying with diisopropyl ether.

1 - (2,5 - Xylyl) - 4 - (4 - phenylpiperazine) - 1 - butanol melting at about 92.8—93.8° C. after recrystallisation from acetone and water.

1 - (4 - Tolyl) - 4 - [4 - (4 - tolyl)piperazine] - 1 - butanol melting at about 105—106° C. after purifying with diisopropyl ether.

1 - (4 - Tolyl) - 4 - [4 - (4 - Anisyl)piperazine] - 1 - butanol melting at about 84—85° C. after recrystallisation from acetone and water.

1 - (4 - Fluorophenyl) - 4 - (4 - phenylpiperazine) - 1 - butanol melting at about 85.5—87.5° C.

1 - (4 - Fluorophenyl) - 4 - (4 - phenylpiperazine) - 1 - butanol hydrochloride melting at about 143.5—146.5° C.

1 - (4 - Chlorophenyl) - 4 - (4 - phenylpiperazine) - 1 - butanol melting at about 93.5—95° C.

1 - (4 - Fluorophenyl) - 4 - [4 - (3 - chlorophenyl)piperazine] - 1 - butanol melting at about 100—101.8° C. after recrystallisation from acetone.

1 - (4 - Fluorophenyl) - 4 - [4 - (4 - chlorophenyl)piperazine] - 1 - butanol melting at about 112.5—113.8° C. after recrystallisation from diisopropyl ether.

1 - (4 - Chlorophenyl) - 4 - [4 - (3 - chlorophenyl)piperazine] - 1 - butanol melting at about 84—85° C. after recrystallisation from diisopropyl ether.

1 - (4 - Chlorophenyl) - 4 - [4 - (4 - chlorophenyl)piperazine] - 1 - butanol melting at about 132—133° C. after recrystallisation from a mixture of diisopropyl ether and acetone.

1 - (4 - Fluorophenyl) - 4 - [4 - (2-anisyl)-piperazine] - 1 - butanol melting at about 105—106° C. after recrystallisation from diisopropyl ether.

1 - (4 - Chlorophenyl) - 4 - [4 - (3 - tolyl)-piperazine] - 1 - butanol melting at about 93—94.5° C. after recrystallisation from diisopropyl ether.

1 - (4 - Chlorophenyl) - 4 - [4 - (4-tolyl)-piperazine] - 1 - butanol melting at about 116—117° C. after recrystallisation from diisopropyl ether.

1 - (4 - Fluorophenyl) - 4 - [4 - (4 - tolyl)-piperazine] - 1 - butanol melting at about 93—95° C.

1 - (4 - Anisyl) - 4 - (4 - phenylpiperazine)-1-butanol melting at about 104.2—107.2° C.

1 - (4 - Anisyl) - 4 - [4 - (2 - chlorophenyl)-piperazine] - 1 - butanol melting at about 106.8—108.4° C.

1 - (4 - Anisyl) - 4 - [4 - (3 - tolyl)piperazine] - 1 - butanol melting at about 119.5—121.5° C. after recrystallisation from diisopropyl ether.

1 - (4 - Anisyl) - 4 - [4 - (4 - tolyl)piperazine] - 1 - butanol melting at about 109.5—110.2° C. after recrystallisation from a mixture of ether and acetone.

1 - (4 - Ethoxyphenyl) - 4 - (4 - phenylpiperazine)-1-butanol melting at about 113—114.8° C. after recrystallisation from diisopropyl ether.

1 - Phenyl - 4 - [4 - (2 - pyridyl)piperazine] - 1 - butanol melting at about 113.8—114.8° C. after recrystallisation from diisopropyl ether.

1 - (4 - Fluorophenyl) - 4 - [4 - (2 - pyridyl)piperazine] - 1 - butanol melting at about 104—105° C.

1 - (4 - Tolyl) - 4 - [4 - (2 - pyridyl)-piperazine] - 1 - butanol melting at about 119.2—119.8° C. after recrystallisation from diisopropyl ether.

1 - Phenyl - 4 - [4 - (4 - methyl - 2-pyrimidyl)piperazine] - 1 - butanol melting at about 78.5—80° C. after recrystallisation from diisopropyl ether.

1 - (2 - Thienyl) - 4 - (4 - phenylpiperazine) - 1 - butanol melting at about 91.4—93° C. after recrystallisation from diisopropyl ether.

1 - (2 - Thienyl) - 4 - [4 - (3 - tolyl)-piperazine] - 1 - butanol melting at about 76—78° C. after recrystallisation from ether.

1 - (2 - Thienyl) - 4 - [4 - (4 - tolyl)piperazine] - 1 - butanol melting at about 113—114° C. after recrystallisation from diisopropyl ether.

1 - (2 - Thienyl) - 4 - [4 - (3 - fluorophenyl)piperazine] - 1 - butanol melting at about 78—79° C. after recrystallisation from diisopropyl ether.

1 - (2 - Thienyl) - 4 - [4 - (4 - chlorophenyl)piperazine] - 1 - butanol melting at about 109.2—110° C. after recrystallisation from a mixture of acetone and water.

1 - (2 - Thienyl) - 4 - [4 - (2 - chlorophenyl)piperazine] - 1 - butanol melting at about 85.5—87.5° C.

1 - (2 - Thienyl) - 4 - [4 - (3 - chlorophenyl)piperazine] - 1 - butanol melting at about 81.5° C. after recrystallisation from a mixture of acetone and water.

1 - (2 - Thienyl) - 4 - [4 - (4 - chlorophenyl)piperazine] - 1 - butanol melting at about 110—111.9° C. after recrystallisation from acetone.

1 - (2 - Thienyl) - 4 - [4 - (2 - pyridyl)-piperazine] - 1 - butanol melting at about 95—97° C. after recrystallisation from diisopropyl ether.

1 - (2 - Thienyl) - 4 - [4 - (2 - pyrimidyl)-piperazine] - 1 - butanol melting at about 97.6—99.4° C. after recrystallisation from diisopropyl ether.

EXAMPLE 11.

A mixture of 6.2 parts of γ-chloro-4-methoxy-butyrophenone and 8.9 parts of 1-(6 - methyl - 2 - pyridyl)piperazine was heated on an oil bath at 110° C. for 8 hours. On cooling, the mixture was partitioned between ether and water. The organic layer was separated, treated with diisopropyl ether and petroleum ether, and chilled to yield 1-[γ-(4-anisoyl)propyl] - 4 - (6 - methyl - 2 - pyridyl)-piperazine melting at about 74—76° C.

EXAMPLE 12.

A mixture of 14.8 parts of 1-(γ-benzoyl-propyl)piperazine, 5 parts of 3-chloro-6-methylthiopyridazine, 120 parts of toluene, and 0.01 parts of potassium iodide was heated in a sealed tube for 48 hours at 140—150° C. and cooled. The organic layer was washed with water, dried, and chilled at −20° C. to yield 1 - (γ - benzoylpropyl) - 4 - (6 - thiomethyl - 3 - pyridazine)piperazine melting at about 124—125° C.

EXAMPLE 13.

To 119 parts of N - (β - hydroxyethyl)--N-(β-hydroxypropyl)amine and 54 parts of sodium carbonate in 450 parts of water heated to 70° C. were added 190.5 parts of 4-toluene - sulphonyl chloride. This mixture was heated to 95° C. for 1 hour, cooled to 0° C., and then filtered. The filtercake was extracted with ether. The ether was evaporated and the residue recrystallised first from a mixture of 2-propanol and petroleum ether by chilling at −20° C. and then from a mixture of ethanol and acetone to yield N - (4 - toluenesulphonyl) - N - (β - hydroxyethyl) - N - (β - hydroxypropyl)amine melting at about 66.2—68.2° C.

A mixture of 450 parts of this product and 690 parts of thionyl chloride was heated to 125° C. for 1 hour, cooled and the excess of thionylchloride evaporated. The residue was purified by addition of toluene and evaporation of this solvent to yield N - (4 - toluenesulphonyl) - N - (β - chloroethyl) - N - (β-chloropropyl) - amine. To a hot stirred mixture of 31 parts of this product, 32 parts of sodium carbonate, 0.1 parts of potassium iodide, and 215 parts of cyclohexanol was added portionwise a solution of 9.3 parts of aniline in 15 parts of cyclohexanol. After refluxing for 48 hours, the mixture was cooled and filtered. The filtrate was diluted with benzene, ether, water, and concentrated hydrochloric acid. The solid which precipitated was collected on a filter and dried to yield 1-(4-toluene - sulphonyl) - 3 - methyl - 4 - phenylpiperazine hydrochloride melting at about 214—220° C. with decomposition.

A mixture of 93.5 parts of the foregoing product, 71.7 parts of phenol, and 570 parts of a solution of a solution of 30% hydrogen bromide in acetic acid was stirred for 24 hours at 30° C. The solid was collected on a filter, washed with ether, and then triturated with boiling acetone to yield 3-methyl-4-phenylpiperazine dihydrobromide melting at about 193.4—199° C. with decomposition.

The free base of 3 - methyl - 4 - phenylpiperazine dihydrobromide was liberated by dissolving 15.7 parts of the salt in water, rendering the solution alkaline, extracting the solution with ether, and evaporating the ether extract. The residue was dissolved in 120 parts of 4 - methyl - 2 - pentanone and this solution was then refluxed with 11.2 parts of γ - chloro - 4 - fluorobutyrophenone, 12.7 parts of sodium carbonate, and 0.1 part of potassium iodide for 22 hours. After filtration, the filtrate was treated with activated charcoal and then evaporated. The oily residue was dissolved in ether and this solution was saturated with hydrogen chloride gas. The precipitate was collected on a filter and then recrystallised from boiling 2-propanol to yield 1 - [γ - (4-fluorobenzoyl)propyl] - 3 - methyl - 4-phenylpiperazine dihydrochloride melting at about 227—234.5° C. with decomposition.

By substituting the appropriate materials in the above procedure, the following compounds were obtained:

1 - (γ - Benzoylpropyl) - 3 - methyl - 4-phenylpiperazine dihydrochloride melting at about 229—233° C.

1 - [γ - (4 - Anisoyl)propyl] - 3 - methyl-4 - phenyl - piperazine melting at about 92—93.8° C.

1 - [γ - (2 - Thenoyl)propyl] - 3 - methyl-4-phenylpiperazine dihydrochloride melting at

about 214—215.5° C.

1 - (γ - Benzoylpropyl) - 3 - methyl - 4-(2-anisyl)piperazine dihydrochloride melting at about 212—215° C.

1 - [γ - (4 - Fluorobenzoyl)propyl] - 3-methyl - 4 - (2 - anisyl)piperazine dihydrochloride melting at about 212—213° C.

1 - [γ - (4 - Anisoyl)propyl] - 3 - methyl-4 - (2 - anisyl)piperazine dihydrochloride melting at about 199—200° C.

1 - [γ - (2 - Thenoyl)propyl] - 3 - methyl-4 - (2 - anisyl)piperazine dihydrochloride melting at about 213—214.5° C.

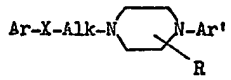
EXAMPLE 14.

To a solution of 211 parts of 4 - anisyl magnesium bromide in 700 parts of ether was added dropwise with stirring, a solution of 180.9 parts of 1 - phenyl - 4 - cyanopropyl-piperazine in 700 parts of ether at such a rate that gentle refluxing is maintained. Refluxing was continued for about one hour, then the reaction mixture was acidified carefully by the addition of dilute hydrochloric acid.

The aqueous acidic layer was separated, warmed gently for about an hour, made alkaline by the addition of dilute aqueous sodium hydroxide, and extracted with chloroform. The organic solution was dried over anhydrous potassium carbonate, then concentrated to dryness to afford 1 - [γ - (4 - anisoyl)-propyl] - 4 - phenylpiperazine melting at about 85—86.2° C.

WHAT I CLAIM IS:—

1. Compounds of the general formula:



wherein Alk is an alkylene radical containing 3 or 4 carbon atoms; R is hydrogen or a methyl radical; X is a carbonyl or hydroxymethylene radical; Ar is a phenyl, tolyl, xylyl, halophenyl, alkoxyphenyl, or thienyl radical; and Ar^1 is a phenyl, tolyl, xylyl, halophenyl, alkoxyphenyl, benzoyl, halobenzoyl, alkoxybenzoyl, a trifluoromethylbenzoyl, thenoyl, pyridyl, methylpyridyl, a nicotinyl, pyrimidyl, methylpyrimidyl, 2-thiazolyl, 2-methylthiazolyl, 2-(1,3,4-thiadiazolyl), 5-(1,2,4-thiadiazolyl), methylthiadiazolyl, cyanopyridyl, carboxamidopyridyl, dimethylpyrimidyl, methylthiopyridazino, chloropyridazino, or methoxypyridazino radical and pharmaceutically acceptable non-toxic salts thereof.

2. 1 - [γ - (4 - Fluorobenzoyl)propyl] - 4-phenylpiperazine and pharmaceutically acceptable non-toxic salts thereof.

3. 1 - [γ - (4 - Fluorobenzoyl)propyl] - 4-(2 - methoxyphenyl)piperazine and pharmaceutically acceptable non-toxic salts theerof.

4. 1 - [γ - (4 - Fluorobenzoyl)propyl] - 4-(2 - pyridyl)piperazine and pharmaceutically acceptable non-toxic salts thereof.

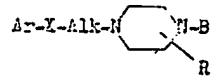
5. 1 - [γ - (4 - Fluorobenzoyl)propyl] - 4-(2 - pyrimidyl)piperazine and pharmaceutically acceptable non-toxic salts thereof.

6. 1 - [γ - (4 - Fluorobenzoyl)propyl] - 4-[2 - (4 - methyl)thiazolyl]piperazine and pharmaceutically acceptable non-toxic salts thereof.

7. 1 - [γ - (2 - Thenoyl)propyl] - 4-phenylpiperazine and pharmaceutically acceptable non-toxic salts thereof.

8. 1 - (γ - Benzoylpropyl) - 4 - (2 - chlorobenzoyl)piperazine and pharmaceutically acceptable non-toxic salts thereof.

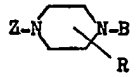
9. A process for the preparation of compounds of the general formula:



wherein Alk is an alkylene radical containing 3 or 4 carbon atoms; R is hydrogen or a methyl radical; X is a carbonyl or hydroxymethylene radical; Ar is a phenyl, tolyl, xylyl, halophenyl, alkoxyphenyl, or thienyl radical; B is hydrogen or a phenyl, tolyl, xylyl, halophenyl, alkoxyphenyl, benzoyl, halobenzoyl, alkoxybenzoyl, trifluoromethylbenzoyl, thenoyl, pyridyl, methylpyridyl, nicotinyl, pyrimidyl, methylpyrimidyl, 2-thiazolyl, 2-methylthiazolyl, 2 - (1,3,4 - thiadiazolyl), 5-(1,2,4-thiadiazolyl), methylthiadiazolyl, cyanopyridyl, carboxamidopyridyl, dimethylpyrimidyl, methylthiopyridazino, chloropyridazino, or methoxypyridazino radical and pharmaceutically acceptable non-toxic salts thereof; which comprises heating a compound of the general formula:

Ar—Y

with a compound of the general formula:



wherein R and B are defined as above and Y is X—Alk—Halogen or Mg—Halogen and Z is hydrogen or, where Y is Mg—Halogen, NC—Alk— followed, if desired, in the case where B is hydrogen, by reacting the product with a compound of the general formula:

Halogen—Ar^1

wherein Ar^1 is a phenyl, tolyl, xylyl, halophenyl, alkoxyphenyl, benzoyl, halobenzoyl, alkoxybenzoyl, trifluoromethylbenzoyl, thenoyl, pyridyl, methylpyridyl, nicotinyl pyrimidal, methylpyrimidal, 2-thiazolyl, 2-methylthiazolyl, 2 - (1,3,4 - thiadiazolyl), 5 - (1,2,4-thiadiazolyl), methylthiadiazolyl, cyanopyridyl, carboxamidopyridyl, dimethylpyrimidal, methylthiopyridazino, chloropyridazino or methoxypyridazino radical and/or in the case where X in the product is a carbonyl group, by reduction of this to a hydroxymethylene group by means of a metal hydride of the general formula (alkali metal) MH_4 where M is boron or aluminium.

10. A process for the preparation of 1-[γ-(4 - fluorobenzoyl)propyl] - 4 - phenylpiper-

azine which comprises heating γ - chloro - 4-fluorobutyrophenone with at least one equivalent of 1-phenylpiperazine.

11. A process for the preparation of 1-[γ-(4 - fluorobenzoyl)propyl] - 4 - (2 - methoxyphenyl)piperazine which comprises heating γ-chloro - 4 - fluorobutyrophenone with at least one equivalent of 1 - (2 - methoxyphenyl)-piperazine.

12. A process for the preparation of 1-[γ-(4 - fluorobenzoyl)propyl] - 4 - (2 - pyridyl)-piperazine which comprises heating γ-chloro-4-fluorobutyrophenone with at least one equivalent of 1-(2-pyridyl)piperazine.

13. A process for the preparation of 1-[γ-(4 - fluorobenzoyl)propyl] - 4 - (2 - pyrimidyl)-piperazine which comprises heating γ-chloro-4-fluorobutyrophenone with at least one equivalent of 1-(2-pyrimidyl)piperazine.

14. A process for the preparation of 1-[γ-(4 - fluorobenzoyl)propyl] - 4 - [2 - (4-methyl)thiazolyl]piperazine which comprises heating γ - chloro - 4 - fluorobutyrophenone with at least one equivalent of 1 - [2 - (4-methyl)thiazolyl]piperazine.

15. A process for the preparation of 1-[γ-(2 - thenoyl)propyl] - 4 - phenylpiperazine which comprises heating 2 - (γ - chlorobutyryl)-thiophene with at least one equivalent of 1-phenylpiperazine.

16. A process for the preparation of 1-(γ-benzoylpropyl) - 4 - (2 - chlorobenzoyl)-piperazine which comprises heating 1 - (γ-benzoylpropyl)piperazine with at least one equivalent of 2-chlorobenzoyl chloride.

17. A process for the preparation of 1-aryl-alkyl - 4 - arylpiperazine and pharmaceutically acceptable non-toxic salts thereof substantially as described with reference to any one of the Examples.

18. 1 - Arylalkyl - 4 - arylpiperazine and pharmaceutically acceptable non-toxic salts thereof when prepared by the process claimed in any one of the preceding claims 9 to 17.

19. 1 - (4 - Fluorophenyl) - 4 - [4 - (2-anisyl)piperazine] - 1 - butanol and pharmaceutically acceptable non-toxic salts thereof.

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